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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,166	08/08/2005	Christoph Burkhardt	PD/4-32516A	4328

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EXAMINER

SINGH, ANOOP KUMAR

ART UNIT PAPER NUMBER

1632

DATE MAILED: 09/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/529,166	Applicant(s) BURKHART ET AL.	
	Examiner Anoop Singh	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 1-3,6,7,9 and 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4, 5 and 8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/24/05; 8/8/05</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of claim 4, 5 and 8 (group II) in the reply filed on July 25, 2006 is acknowledged.

Claims 1-3, 6-7 and 9-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 25, 2006.

Claims 4, 5 and 8 are under consideration.

Claim Objections

Claim 4 is objected to because of the following informalities: Instant claim does not recite section (a) in correct syntax. Punctuation between MHC class II restricted T cell receptor and a MHC restricted... would obviate this objection. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge

pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

Claims 5 and 8 are broad in scope. The following paragraph will outline the full scope of the claims.

These claims are broad in scope, encompassing using any agent identified by method disclosed in claim 4 as pharmaceuticals. Claim 8 is directed to any pharmaceutical composition comprising at least one agent that interferes with T cell activation and or differentiation identified by the method of claim 4. The disclosure provided by the applicant, in view of prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to a reasonable extent so that one of the ordinary skills in the art at the time of invention by applicant would be able to practice the invention without any undue burden being on such Artisan.

The claims are directed to the use of an agent identified by the method of claim 4 as pharmaceuticals and a pharmaceutical composition comprising at least one agent that interferes with T cell activation and or differentiation and modulation of other inflammatory effector cells identified by the method of claim 4.

The invention features a screening assay for identifying an agent that interferes with T cell activation and/or -differentiation and/or modulation of other inflammatory effector cells. See the specification at page 1 in lines 1-3.

The specification asserts the method set forth in the specification to identify candidate compounds that interferes with T cell function includes oligo-peptides, polypeptides,

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proteins, antibodies, (peptide-) mimetic, small molecules, e.g. low molecular weight compounds (LMW's) (see pages 5, lines 24-35). The specification further asserts that an agent identified by the method recited in claim 4 may exhibit pharmacological activity therefore could be useful as a pharmaceutical in the treatment of diseases which are mediated by T-cell and/or inflammatory effector cell derived mediators such as allergic disease, transplantation and autoimmune disease. It is noted that specification further describes the agent of the present invention for use as a pharmaceutical for the treatment of these disease (see page 7, lines 14-35). While the specification has contemplated that methods of the invention may be used to identify an agent that interferes with the T cell function of a mouse, the guidance provided by the specification does not correlated to any specific pharmaceutical.

Claims 5 and 8 embrace a pharmaceutical composition and use of said pharmaceutical identified by the method disclosed in the specification. The specification only provides prophetic reference to the pharmaceutical or agents for screening without giving any sequence/structure information of the molecule itself. The specification also fails to provide any information for the structure or sequence of oligo or polypeptides with contemplated biological activity *in vivo*. The example provides evidence to support the notion that administration of OVA 323-339 peptide results in induction of serum cytokine levels in a dose dependent manner (see page 18 and 22). However, this disclosure does not provide sufficient details to enable one skilled in the art to recreate and identify all possible pharmaceutical agent and their respective use using the method disclosed in the instant invention as prophetically taught in the specification for

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identifying such a pharmaceutical agent, particularly as the structure function relationship of such a pharmaceutical agent and its use is not known. It is apparent that each pharmaceutical for its use in a specific condition would require further experimentation that is not routine and subject to variation in anticipated effect on T-cell mediator in serum. For instance, specification contemplates using oligo or polypeptide without providing any specific structure of such a polypeptide. Ngo et al teaches that addition or deletion, which are critical to maintain the protein structure/function will require guidance (Ngo et al., 1994, The protein Folding Problem and Tertiary Structure Prediction, pp492-495). It is well known in the art to those skilled in the art at the time invention was made that a minor structural difference in compositions could result in substantially different pharmacological activities. The specification has failed to provide guidance or working examples correlating any agent as pharmaceutical to any disease or condition that is identified with the method disclosed in the invention. Finally, it would be unpredictable if any pharmaceutical agent could function to treat any condition as contemplated in the claims. Given the lack of guidance provided by the specification it would have required undue experimentation to make and use of a pharmaceutical to be used in a specific disease condition for one of skill in the art without a reasonable expectation of success.

In conclusion, in view of breadth of the claims and absence of a strong showing by applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions. The specification and prior art do not teach a specific

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pharmaceutical or its use as required by the claims. An artisan of skill would have to perform undue experimentation to practice the method as claimed because the art of identifying a therapeutic agent for the treatment of specific condition was unpredictable at the time of filing of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are directed to a pharmaceutical composition comprising at least one agent that interferes with T cell activation and using such an agent identified by method of screening as a pharmaceuticals. In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification contemplated using a genus of compounds as pharmaceuticals that could be used in variety of disease. The specification discloses that any oligopeptides, polypeptides, proteins, antibodies, (peptide-)mimetics, small molecules can be used as pharmaceutical which has an effect on T cell activation and/or -differentiation and/or

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modulation of other inflammatory effector cells (see specification page 5, lines 24-35).

However, the as filed specification does not disclose a genus of agents that can be used as pharmaceutical that could interfere with T cell activation. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential structures of molecules that are essential for a genus of agents as pharmaceuticals to be used to treat variety of conditions; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular or chemical structures of agents as pharmaceuticals that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of agents as pharmaceuticals to be used in the treatment of variety of condition in a subject. The claimed invention as a whole is not adequately described if the claims require essential or critical elements or structure, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming an unspecified genus of agent as pharmaceutical that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so does not comply with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear

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depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of agent as pharmaceutical that must exhibit the contemplated biological functions of interfering with T cell activation, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recite a limitation "according to" that simply requires to bring into agreement. Since, according only implies a level of agreement between two, thus meets and bound of instant claim 4 is unclear and this limitation does not further limit the instant claim. It is emphasized that more specific reference to the treated mice will

obviate this rejection. Claim 5 and 8 depend on claim 4. Appropriate correction is required.

Claims 4, 5 and 8 are vague and indefinite because instant claims are directed to “determining the level of a T-cell and/or inflammatory effector cell derived mediator in serum of a mouse”. It is emphasized that “derive” can have a broad range of interpretations. Given the breadth of the definition of “derived”, the metes and bounds of the mediator in serum are unclear. Further, it appears to omit essential steps if claims intend to “derive” mediators effector cells. In addition, more to issue, the meets and bound are indefinite because how similar or different material is cannot be clearly determined. Claim 5 and 8 depends on claim 4. Appropriate correction is required.

Claim 5 provides for the use of an agent identified in claim 4, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 5 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4, 5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Knott et al (Am J Respir Crit Care Med. 2000; 161(4 Pt 1): 1340-8 of the record).

Knott et al (Am J Respir Crit Care Med. 2000; 161(4 Pt 1): 1340-8) teach homozygous, naive $\alpha\beta$ -TCR transgenic Balb/c that are sensitized to OVA (see page 1340, column 2, last paragraph). In another experiment, Knott et al disclose administering compound (rat anti mouse CD4 or CD8) prior to OVA aerosol exposure. In addition, Knott et al teach administration of anti-IFN-gamma, 30 minutes prior to OVA aerosol. Knott also teach measuring IgE in serum to determine humoral immunity present in serum by comparing the levels of IgE in wild type and DO11.19 mice. Thus, it is apparent that Knott taught a method to identify agent that interferes with T-cell activation by measuring IgE levels in serum. It is noted that the method of independent claim, claim 4 recite four steps: (a) administering OVA peptide, (b) administering compound before or after OVA (c) determining the levels of inflammatory effector mediator in serum and comprising the levels and selecting the agent. Accordingly, the invention of claim 4 is anticipated by Knott et al because steps recited in the invention are the same as those taught by the cited arts.

Claims 4, 5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al (Biol Pharm Bull. 1995; 18(6): 854-8).

Claim 8 is a product by process claim.

It is noted that as recited claim 4 reads on a method of identifying agent that interferes with T cell activation in any wild type mouse that expresses a MHC class I or MHC class II restricted T cell receptor.

Kim et al teach a mouse model of oral tolerance to ovalbumin (OVA) to determine the modulators of the tolerance and screen selected immuno-modulating substances, cyclophosphamide (CP), Escherichia coli lipopolysaccharide (LPS) and cadmium chloride (Cd). Kim et al teach administering 20 mg OVA to the mice and then these mice are immunized with an i.p. injection of 0.1 mg OVA. It is noted that Kim et al teach the effects of oral OVA and agents on systemic immunity by measuring the immunoglobulin (Ig) levels in serum collected 7 or 14 days after immunization. Kim et al further show screening of modulators of the tolerance by administering cyclophosphamide prior to oral OVA, or 5 consecutive daily oral administrations of LPS after oral OVA elevated or reduced serum levels of anti-OVA IgG mice. It is noted that Kim discloses the levels of IgG subclasses in serum (see abstract). It is noted that the method of independent claim, claim 4 and those in cited art appears to be same. Further, Kim et al teach identification of agents that could be used as modulator for oral tolerance. Accordingly, Kim et al anticipate claims 4, 5 and 8.

Claims 5 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Morris et al (Current Opinion in Immunology, 1991, 3: 748-751, IDS).

Claim 8 is a product by process claim.

Morris et al disclose FK506 has more potent biological activity than cyclosporine that inhibits the production of various cytokines IL-2, -3, -4 and gamma and suppresses the appearance of IL-2 receptor on activated T cell both *in vivo* and *in vitro* (see page 749, column 1, paragraph 4). Thus, FK506 and cyclosporine would inherently interfere with T cell activation in any method including one recited in instant disclosure. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Accordingly, Morris anticipates claim 8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 4-5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Castro et al (J Exp Med. 2000; 192(10): 1529-34) and Sharif et al (Nature Medicine, 2001, 7, 1057 – 1062).

Castro et al teach a method wherein spleen cell suspension from DO11.10 transgenic mice is injected intravenously into syngeneic BALB/c recipients such that CD4⁺ T cells are adoptively transferred. It is noted that these mice would account most of the T cell in lymph node after priming would express MHC class II restricted T cell receptor. Furthermore, mice are primed for 2 days after adoptive transfer with either OVA₃₂₃₋₃₃₉ (7 or 200 µg) or OVA (LPS/endotoxin) (200 µg or 5 mg) (see materials and method, page 1530, column 2, paragraph 2). Castro et al further describe injecting mice a compound intraperitoneally with anti-IL-10R (0.5 mg) mAb. Castro et al also describe determining the levels of OVA-specific IgG1 and IgG2a in micro titer plate using serum

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Isotype ELISA (see page 1530, column 2, paragraph 5) and teach measuring IFN-gamma, IL-4 and IL-10 by ELISA in T cell and antigen presenting cell (see page 1530, column 2, paragraph 3 and 4). Thus, Castro et al teach a method of administering to a mouse wherein majority of T cell express MHC class II restricted receptor, a OVA-peptide and ova with or without anti-IL-10R mAb and determined the difference in level of effector mediators and thus evaluating the role of IL-10R mAb. Castor et al identified the role of anti IL-10 receptor Ab in vaccine development using the method recited in the instant application (see abstract and page 1533, column 1). It would be inherent that any agent (anti IL-10mAb) that is identified by the method of Castro and the composition of Castro and those embraced by the instant claims appear to be structurally same. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

However, Castro et al do not explicitly teach measuring the levels of T-cell and/or inflammatory effector cell derived mediator in serum of the mouse.

Prior to the instant invention, measuring level of T-cell or inflammatory effector cell derived mediator in serum and cell culture by ELISA was routine in the art. The uses for ELISA based assay to determine the cytokine levels of inflammatory cell derived mediator known in the art at the time the claimed invention was made included serum as well as cell extracts and culture supernatant. Sharif et al disclose using ELISA to measure cytokines and antibody isotype specific for GAD or OVA, as in culture supernatants and in serum (see page 1061, column 2, paragraph 4 and 5). In addition, Sharif et al also taught a method to determine the level of IFN-gamma and IL-4 in serum (see Figure 1, page 1058) and comparing the levels in serum to wild type control animal (see figure 1). However, Sharif et al do not explicitly teach measuring cytokine level in TCR transgenic mouse.

Accordingly, in view of the teachings of Castro, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to determine the levels of T cell derived mediator in serum of the mouse taught by Castro using a ELISA with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Castro had already shown the modulation of IL-4, IFN- gamma in T cell and AP cell (see page 1530, column 2, paragraph 3-4) and particularly since Sharif disclosed that it was routine to determine the level of cytokine in serum, tissue extract and cell supernatants. Although Castro did not disclosed measuring cytokine level in serum, he generally embraced potential of measuring OVA-specific serum isotype. Therefore, given that routine methods were available to determine serum cytokine level as per the teaching of Sharif, it would have

obvious for an Artisan to use the method of Castro to screen compounds by comparing the levels of IL-4 and IFN-gamma in serum as disclosed in the instant application.

One who would practiced the invention would have had reasonable expectation of success because Castro et al had already described a method to screen agent that interferes with Tcell activation. Sharif had already described use of ELISA based assay to determine the levels of cytokine in serum as well as cell that could have been used in any method to compare the cytokine levels. Thus, it would have only required routine experimentation to modify the method disclosed by Castro to include measuring the cytokine levels in serum to compare with control animal as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 4-5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knott et al (Am J Respir Crit Care Med. 2000; 161(4 Pt 1): 1340-8 of the record); Castro et al (J Exp Med. 2000; 192(10): 1529-34) and Sharif et al (Nature Medicine, 2001, 7, 1057 – 1062).

The combined teachings of Castro et al, Sharif et al have been discussed above and relied in same manner. However, none of the references explicitly teaches administering OVA peptide directly to TCR transgenic mouse .

Knott et al (Am J Respir Crit Care Med. 2000; 161(4 Pt 1): 1340-8) teach homozygous, naive $\alpha\beta$ -TCR transgenic Balb/c that are sensitized to OVA (see page 1340, column 2, last paragraph). In another experiment, Knott et al disclose

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administering compound (rat anti mouse CD4 or CD8) prior to OVA aerosol exposure. In addition, Knott et al teach administration of anti-IFN-gamma 30 minutes, prior to OVA aerosol. Knott also teach measuring IgE in serum to determine humoral immunity present in serum by comparing the levels of IgE in wild type and DO11.19 mice. Thus, it is apparent that Knott taught a method to identify agent that interferes with T-cell activation by measuring IgE levels in serum. It is noted that the method of independent claim, claim 4 recite four steps: (a) administering OVA peptide, (b) administering compound before or after OVA (c) determining the levels of inflammatory effector mediator in serum and comprising the levels and selecting the agent. Accordingly, the invention of claim 4 is anticipated by Knott et al because steps recited in the invention are the same as those taught by the cited arts.

Accordingly, in view of the teachings of Knott, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method of Knott to determine the levels of T cell derived mediator in serum of the using the treatment regimen disclosed by Castro to measure cytokine levels taught by Sharif with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as Knott had already shown that aerosol exposure of OVA show of IL-4, IFN- in BALF of DO11.10 transgenic and wild type mouse (see Figure 3) and particularly since Sharif disclosed that it was routine to determine the level of cytokine in serum, tissue extract and cell supernatants. Although Knott did not disclosed measuring cytokine level in serum and used a purified OVA₃₂₃₋₃₃₉ peptide, he generally embraced potential of measuring humoral response

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after exposure of OVA in serum. Therefore, given that routine methods were available to determine serum cytokine level as per the teaching of Sharif, and availability of purified OVA₃₂₃₋₃₃₉ peptide, it would have obvious for an Artisan to modify the method of Knott to screen compounds by comparing the levels of IL-4 and IFN-gamma in serum and using purified OVA₃₂₃₋₃₃₉ peptide as disclosed in the instant application. The skilled Artisan would have further motivated to optimize different treatment regimen and steps to optimize the screening method to identify agents that would have interfered with T cell activation (see MPEP 2144.04).

One who would practiced the invention would have had reasonable expectation of success because Knott et al had already described a method to screen agent that interferes with T-cell activation. Sharif had already described use of ELISA based assay to determine the levels of cytokine in serum as well as cell that could have been used in any method to compare the cytokine levels. Thus, it would have only required routine experimentation to modify the method disclosed by Knott to include measuring the cytokine levels in serum to compare with control animal as required by instant invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

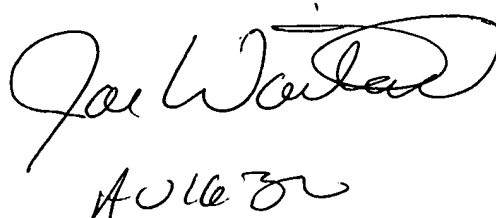
No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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